4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2021-D-1140]

Investigational New Drug Application Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations; Draft Guidance for Sponsor-Investigators; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for sponsor-investigators entitled "IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations." FDA is publishing this draft guidance to provide sponsor-investigators (hereafter referred to as sponsors) who are interested in developing individualized antisense oligonucleotide (ASO) drug products for a rapidly progressive, severely debilitating, or life-threatening (SDLT) genetic disease (caused by a unique genetic variant or variants), with clinical recommendations for submission of investigational new drug applications (INDs). These recommendations specifically address the following clinical considerations: ethical and human subject protection, diagnostic and genetic, dosing, administration, safety, and assessment of clinical response to treatment.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2021-D-1140 for "IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow

the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Hobart Rogers, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 51, Rm 3114, Silver Spring, MD 20903-0002, 301-796-2213.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for sponsor-investigators entitled "IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations." FDA is publishing this draft guidance to provide sponsor-investigators (hereafter referred to as sponsors) who are interested in developing individualized ASO drug products for a rapidly progressive SDLT genetic disease (caused by a unique genetic variant or variants), with clinical recommendations for submission of INDs. These recommendations specifically address the following clinical considerations: ethical and human subject protection, diagnostic and genetic, dosing, administration, safety, and assessment of clinical response to treatment.

This draft guidance describes clinical considerations and, when applicable, important information to include in IND submissions for such ASO drug products for a small number of participants (typically one to two) with SDTL diseases. In general, ASO drug products referred

to in this draft guidance belong to a well-characterized chemical class and for which there is considerable nonclinical and clinical experience that is publicly available or to which the sponsor has a right of reference. The draft guidance discusses considerations and information to submit in an IND regarding: (1) confirmation of the participant's genetic diagnosis and genetic variant(s) targeted by the ASO drug product, (2) the requirements and procedures for informed consent of the participant, (3) appropriate and safe dosing and administration procedures that are detailed and supported by relevant nonclinical evidence, (4) the nature and schedule of the specific safety assessments (adverse events and laboratory testing) to be conducted, and (5) methods for continuous clinical monitoring (e.g., via clinical outcome assessments, pharmacodynamic biomarkers) of the participant to evaluate and document their clinical response(s) and to allow for an informed benefit-risk determination. This draft guidance is expected to facilitate the preparation of adequate and complete IND submissions for investigational ASO drug products for participants with SDLT diseases targeted by the specified ASO drug product.

This draft guidance represents one guidance in a series of guidances that FDA intends to publish to advise and help sponsors planning to use individualized ASO drug products for SDLT diseases caused by unique genetic variant(s) and for whom there are no alternative therapies available to treat their disease.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

While this guidance contains no new collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014. The collections of information in 21 CFR parts 50 and 56 for obtaining informed consent for prospective patients have been approved under OMB control number 0910-0130.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

Dated: December 1, 2021.

Lauren K. Roth,

Associate Commissioner for Policy.

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